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REVIEW

Improving outcomes for operable pancreatic cancer: Is access to safer surgery the problem?

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Abstract

Despite advances in the understanding and treatment of pancreatic cancer in the last two decades, there is a persisting nihilistic attitude among clinicians. An alarmingly high rate of under-utilization of surgical management for operable pancreatic cancer was recently reported in the USA, where more than half of patients with stage 1 operable disease and no other contraindications were not offered surgery as therapy, denying this group of patients a 20% chance of long-term survival. These data indicate that a nihilistic attitude among clinicians may be a significant and reversible cause of the persisting high mortality of patients with pancreatic cancer. This article examines the modern management of pancreatic cancer, in particular, the advances in surgical care that have reduced the mortality of pancreatectomy to almost that of colonic resection, and outlines a strategy for improving outcomes for patients with pancreatic cancer now and in the future.

Introduction

Although there have been advances in the treatment of other gastrointestinal malignancies, pancreatic cancer remains a highly lethal condition. It is the third most common gastrointestinal cancer and the fourth most common cause of cancer death in adult Australians.[1] It has an incidence of nine per 100 000 population and a death-to-incidence ratio approaching one.[2] This is because pancreatic cancer is a very aggressive tumor; the overall 5-year survival rate of less than 5% is the lowest among all types of cancer.

Surgical resection offers the only chance of long-term survival for patients with pancreatic cancer. Current chemotherapy and radiotherapy regimens are only modestly effective and do not offer cure. Patients who undergo surgical resection for localized, non-metastatic adenocarcinoma of the pancreas have a 5-year survival rate of approximately 8–21%[3] and a median survival of 12–22 months.[4] Unfortunately, approximately only 20% of patients have disease amendable to surgical resection at the time of presentation[2] as the majority present with metastatic or locally-advanced disease.

The treatment for resectable pancreatic cancer in the head of the pancreas is a pancreaticoduodenectomy or Whipple's procedure, which was initially described by Allen Oldfather Whipple in 1935.[5] The perioperative mortality rate was 30% in the 1940s,[6] and approximately 25% in the 1960s, which is higher than the disease-specific 5-year survival rate after resection. This led to reports of patients undergoing palliative bypasses having equivalent, if not better overall outcomes than patients who underwent pancreaticoduodenectomy, raising doubts regarding the value of surgery in the treatment of pancreatic cancer.[7–9] With advances in surgical techniques and improvements in anesthetic and perioperative care, the current 30-day in-hospital mortality is less than 5% in high-volume centers.[2,10–15] This approaches the 30-day in-hospital mortality of colorectal cancer resection, which is in the order of 3.9%.[16] Despite the fact that surgery is the only current effective treatment for pancreatic cancer, an alarming US report was published recently on the under-utilization of surgery in the case of clearly operable pancreatic cancer. Specifically, more than half of patients with early disease, the ones who had the most potential to benefit from resection, were not even offered the option of an operation.[17] Bilimoria *et al.* reviewed the National Cancer Database in the USA between 1995–2004 and identified 9559 patients with early and potentially resectable, clinical stage I pancreatic cancer (T1N0M0 and T2N0M0). They found that 71% of patients did not undergo surgery; 6.4% of these cases were excluded due to comorbidity, 4.2% refused surgery, and 9.1% were excluded due to age. This left as many as 38% of patients that were 'not offered surgery'. A further 14% of patients did not undergo surgery, but the reason was not reported in the record. Therefore, a total of 52% of patients with resectable and potentially curable pancreatic cancer without any identifiable contraindications failed to undergo surgery.

The outcomes characterized by the study of Bilimoria *et al.* also demonstrate that the survival of unoperated patients with early stage disease were better than those with more advanced stage disease, thereby confirming that this group had stage 1 pancreatic cancer and was not misclassified. Clearly these figures are of concern. Although the historical 25% mortality rate for pancreaticoduodenectomy may justify a lack of enthusiasm about the role of surgical resection, modern surgical treatment, when performed in specialist surgical centers, has a mortality rate less than 5%. Based on these data, the authors suggest that a persisting nihilism of clinicians towards pancreatic cancer and pancreatectomy for any neoplastic lesions of the pancreas may be the most significant, correctable factor that contributes to the current poor outcomes of this disease.

Reliable and detailed data concerning the management of pancreatic cancer in Australia are lacking. In the state of New South Wales (NSW) in Australia, approximately 700 patients are diagnosed with pancreatic cancer each year; 25% of these (175 per year) are recorded as 'localized' in the NSW cancer registry. Despite these numbers, data from the NSW Pancreatic Cancer Network (NSWPCN) show that less than 70 patients per year undergo pancreatic resection for pancreatic cancer in the state. It therefore seems likely that similar nihilistic attitudes to potentially curative pancreatic resection may exist in Australia.

Although specialist centers throughout the world publish excellent results, these may not reflect individual clinician's local experiences and may influence management decisions. So how do we overcome this significant issue, and in more general terms, improve the overall outcomes for patients with pancreatic cancer? The published literature suggests that there are four key issues that should be addressed if we are to improve the overall outcomes for patients with this disease: (i) specialist treatment team referral. Patients and their families should be given the opportunity to access the units and clinicians that are most likely to achieve the best results; (ii) improve the quality of multidisciplinary care in hospitals. Critical aspects of such multidisciplinary care include accurate, timely, and consistent staging, stage-specific treatment plans, and multidisciplinary treatment groups comprised of specialized surgeons, medical oncologists, radiation oncologists, radiologists, histopathologists, palliative care specialists, dietitians, and nurse specialists; (iii) ensuring complete surgical resections (R0/R1) of the tumors in all 'resectable' and 'borderline' resectable tumors; and (iv) standardizing evidence-based treatment of premalignant lesions, such as intraductal papillary mucinous neoplasms (IPMN) and mucinous cystic neoplasms (MCN). Details on these issues will be discussed later.

Specialist treatment team referral

Surgical volume–outcome relationships have been recognized for decades,[18–21] but in the past have focused primarily on cardiovascular procedures. More recently, similar studies have addressed cancer surgery. It is now well accepted in many countries, such as the UK,[22–24] that cancer patients should be treated in specialized centers to achieve the best possible outcomes.

Halm *et al.*[25] reviewed 135 such studies, encompassing 27 procedures and clinical conditions. They showed that high volume was associated with better outcomes over a wide range of conditions and procedures. The strongest associations were found for the treatment of AIDS and surgery for pancreatic cancer, esophageal cancer, abdominal aortic aneurysm, and pediatric cardiac conditions (a median of 3.3–13 excess deaths per 100 cases were attributed to low volumes in treatment centers). Out of the 10 studies included in the review, nine demonstrated a significant volume–outcome relationship. The highest median absolute difference in the mortality rate of high versus low volume was for pancreatic cancer surgery; the median difference in mortality was 13% (range 3–18%). A large, national US study by Finlayson *et al.*[26] examined the mortality of resection for eight cancer types in 195 152 patients. A significant difference was identified between low- and high-volume hospitals for pancreatic resection, esophagectomy, and pulmonary lobectomy. It was again demonstrated that the most substantial difference in mortality (13% *vs* 2.5%) was for pancreatic resection. Further, this difference was even greater for older, higher-risk patients.

Birkmeyer *et al.* studied the relationship between treatment volume and long-term survival.[27] In a retrospective cohort of 7229 patients over the age of 65 years undergoing pancreaticoduodenectomy in the USA between 1992 and 1995, the 3-year survival rate at high-, medium-, and low-volume centers was 37%, 29%, and 26%, respectively ($P < 0.01$). In a more recent study, the same authors identified an absolute difference in long-term survival for pancreatic cancer between low- and high-volume centers of 5% at 5 years (11% *vs* 16%, respectively).[28] Overall there is an inverse linear relationship between the case load volume of units and perioperative mortality; those performing two or less Whipple pancreaticoduodenectomies per year have a mortality rate of 20% to those that perform 16 or more who have a mortality rate of ~3%.

Finlayson and Birkmeyer also constructed a Markov decision analysis model to estimate the life expectancy of patients undergoing major cancer resections (pancreas, lung, and colon) at hospitals performing different volumes.[29] They found that life expectancy increased progressively with hospital volume in the case of all three cancers. For pancreatic cancer, where the difference was most pronounced, life expectancy increased linearly from 1.9 years at very low-volume centers to 3.6 years at very high-volume centers. The differences in life expectancy across volume strata were largely attributable to long-term survival and not operative mortality. Other outcome measures, such as length of stay, were also shorter in high-volume centers.[30] Similar findings have also been reported from the UK, Canada, the Netherlands, and Finland.[31–33]

Apart from better outcomes being associated with higher hospital case load volume, better patient outcomes are also associated with surgeons with a higher volume of case loads. Birkmeyer *et al.* assessed the mortality of 474 108 patients who underwent cardiovascular and cancer procedures in the USA in 1998 and 1999.[34] They found that individual surgeon volume was inversely related to operative mortality for all procedures. The adjusted odds ratio for operative death for patients for a low- versus a high-volume surgeon was the highest for pancreatic resection (3.61). Surgeon volume also accounted for 55% of the apparent effect of the hospital volume in pancreatic surgery. Hence, current global opinion is that pancreatic surgery should be performed in high-volume centers by surgeons with a high case load volume.

Improving the quality of multidisciplinary care

Apart from specialist treatment team referral, outcomes for patients with pancreatic cancer can also be improved through holistic, multidisciplinary approaches. These include accurate, consistent, and timely preoperative staging; stage-specific management plans; participation of members of the multidisciplinary team (MDT); and the optimization of postoperative care.

Staging

Non-therapeutic laparotomy is associated with a perioperative morbidity rate of 20–30%, a mean hospital stay of 1–2 weeks, and a median survival after surgery of 6 months.[35–37] Therefore, accurate preoperative staging and assessment of resectability is a critical aspect of the diagnostic evaluation of patients with pancreatic cancer that has implications for the overall quality of life. Historically, resectability was assessed intraoperatively, after the duodenum had been 'kocherized', by palpation to determine the relationship of the tumor to the mesenteric vessels. In the modern era, staging consists of CT imaging and endoscopic ultrasound (EUS) with selective use of diagnostic laparoscopy. Modern multidetector CT, optimized for pancreatic imaging, offers the highest accuracy in assessing pancreatic cancer, and is supplemented by EUS for additional information on vessel invasion, lymph node involvement,[38] and the ability to obtain a fine-needle aspiration biopsy (FNAB) of the tumor. When EUS is combined with FNAB, the specificity and accuracy are greatly increased.[39,40] Magnetic resonance imaging (MRI) can also be used for diagnosis, staging, and assessment of resectability of pancreatic cancer. However, its sensitivity, specificity, and accuracy varies in the literature when compared to modern multidetector CT.[38,41–43] The rapid advancement in CT technology in recent years has diminished the role of MRI for pancreatic cancer, and so current opinion is that MRI at best performs equally when compared to multidetector CT. MRI and magnetic resonance cholangiopancreaticography (MRCP) are developing into useful modalities in the diagnosis and assessment of cystic lesions of the pancreas and other precursor lesions of pancreatic cancer, such as IPMN.

FNAB can be instrumental in diagnosis, especially in difficult scenarios, such as pancreatic lipoma, lymphoma, tuberculosis, sarcoidosis, neuroendocrine tumors, and inflammatory pseudotumors. FNAB and obtaining diagnostic tissue remain vitally important if the individual patient is *not* a candidate for operative resection, but suitable for other therapies. It also offers potential for the preoperative assessment of biomarkers of prognosis and therapeutic responsiveness which are currently being developed.[44] Risk of seeding from EUS–FNAB is extremely low when compared to a percutaneous approach[45] as the needle tract is usually resected with the tumor.[46]

The role of staging laparoscopy is more controversial. A recent review by Pisters *et al.* found interpretation of the literature difficult,[47] largely due to an inconsistent use of high-quality CT and variable reports of resection status; many studies included patients with locally-advanced disease. The authors found that routine laparoscopy may prevent unnecessary laparotomy in 4–13% of patients judged to have resectable disease by high-quality CT. The authors concluded that selective laparoscopy should be used in patients with a higher risk of occult M1 disease, which includes large tumors; lesions of the neck, body, or tail of the pancreas; equivocal radiological findings suggestive of occult M1 disease; and patients with subtle clinical or laboratory findings that suggest more advanced disease. Since the publication of the above review article, further studies reporting a low yield of routine laparoscopy have also supported a selective approach.[48–51]

Multidisciplinary team

All patients with a suspected pancreatic neoplasm should be presented and discussed in a multidisciplinary forum. Patients are typically stratified into having resectable (stage I or II), borderline resectable, locally-advanced (stage III), or metastatic (stage IV) disease. A stage-specific, multidisciplinary treatment plan should be adopted according to local and international guidelines.[52] A suggested management approach from our institution is presented in Figure 1.

Complete surgical resection of tumors

The long-term survival of patients is dependent upon the complete macroscopic resection of the tumor (R0, R1).[53] Patients with grossly incomplete resections (R2) survive less than 1 year,[11,54–59] which is equivalent to patients with locally-advanced, surgically-unresectable (stage III) disease. The refinements of surgical techniques and perioperative care that are associated with low perioperative mortality have led to changes in the criteria for resectability.

A significant proportion of patients with pancreatic cancer present with neither clearly resectable, nor clearly unresectable disease. These tumors are termed 'borderline resectable'. Borderline resectable tumors are those that require some form of vascular resection to achieve clear margins. The National Comprehensive Cancer Network defines these as tumors with severe unilateral superior mesenteric vein (SMV) or portal vein (PV) impingement, short segment SMV occlusion with normal vein above and below, abutment of the superior mesenteric artery (SMA), gastroduodenal artery encasement up to its origin from the hepatic artery, or colon/mesocolon invasion.[52] Patients in this group may have their tumor removed with a synchronous vascular resection. En bloc vascular resection was first introduced more than 30 years ago by Fortner as a more radical resection to improve tumor clearance.[60] This technique has been used safely on appropriately selected patients in many centers.[61–73] A recent systematic review[74] pooled data from 52 studies where a total of 1646 patients underwent synchronous PV/SMV resection. These patients represented 26% of all the patients who underwent pancreatectomy. The types of venous resection were 73% circumferential and 11% lateral wedge resection. Of the circumferential resections, 88% were reconstructed with primary anastomoses, 10% with autologous vein grafts, and 2% with synthetic grafts. The morbidity and mortality rates for venous resection were 42% (9–78%) and 5.9% (0–33%), respectively; the latter was not statistically different to all patients in the series (5.2%). Of the 917 patients with available survival data, the median survival was 13 months, and the 5-year survival was 5.8%. The authors concluded that synchronous venous resection does not increase the morbidity and mortality of pancreatec-

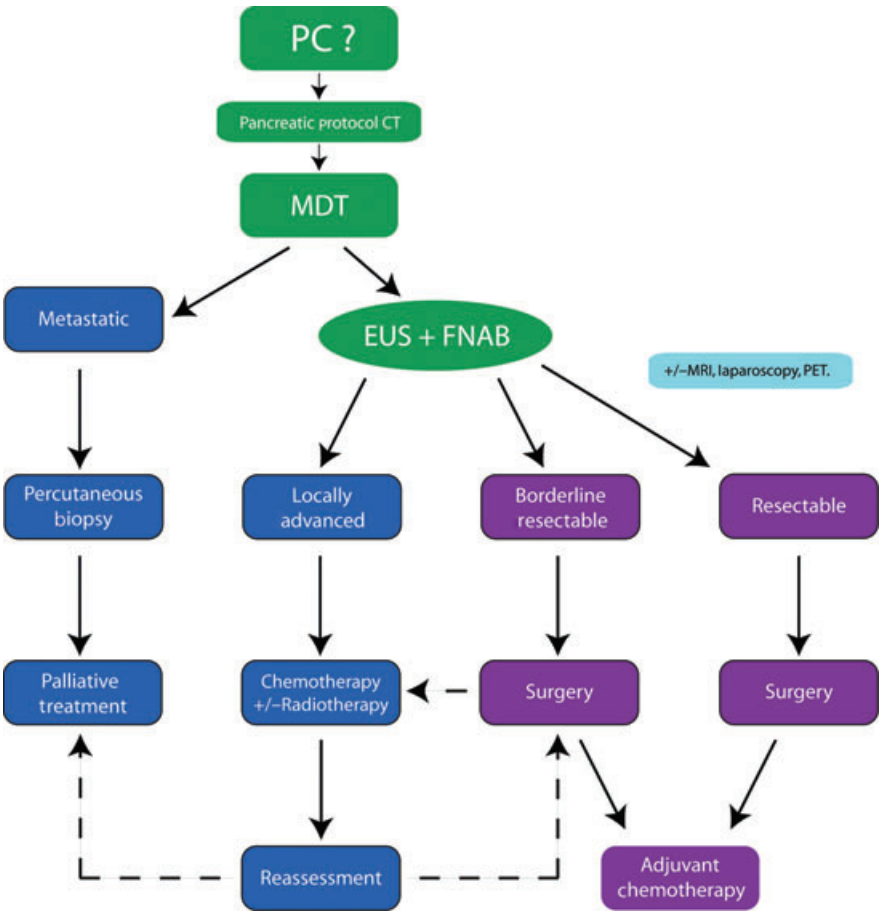

Figure 1 Generic approach to the management of pancreatic cancer (PC) If pancreatic cancer is suspected, then a pancreatic protocol CT scan is required to delineate the vasculature that surrounds the pancreas Multidisciplinary team (MDT) review is recommended at this stage with input from specialist radiologists regarding the extent of disease. Each patient's case should be reviewed by the MDT whenever management decisions are being made If metastatic disease is detected, then percutaneous biopsy is reasonable If not, percutaneous biopsy must be avoided as this renders the patient virtually incurable due to the unacceptable risk of tumor seeding Patients with metastatic disease receive symptom specific palliation or are enrolled into clinical trials of novel therapies If metastatic disease is not detected, endoscopic ultrasound (EUS) assessment with fine-needle aspiration biopsy (FNAB) is advisable both for assessment of the tumor's relationship to the surrounding vasculature and to obtain a tissue diagnosis Combination of a pancreatic protocol CT and EUS will define whether the tumor is locally advanced, resectable, or borderline resectable In select patients, magnetic resonance imaging (MRI), positron emission tomography (PET), and laparoscopy may provide additional information and their utility is determined on a case by case basis, but is not recommended as a routine Resectable and borderline resectable lesions undergo pancreatectomy if there are no other contraindications and receive adjuvant chemotherapy, or are enrolled in clinical trials of novel therapies Patients with locally-advanced disease are usually enrolled in clinical trials that may include radiotherapy, and are reassessed at a later stage as a small number of patients respond, and may be suitable for resection.

tomy and may be performed to achieve margin-negative resections in selected patients with equivalent outcomes, which improves long-term survival.

In contrast, the arterial resection of the encased coeliac axis or SMA carries a much higher mortality and morbidity than venous resection or standard pancreaticoduodenectomy.[73] Gross complete resection cannot be achieved in these patients, likely due to extensive perineural invasion. Hence, they are classified as locally-advanced, surgically unresectable (stage III).

One of the major goals for pancreatic surgery in Australia and throughout the Asia–Pacific region should be to develop specialist units that can offer results comparable to those of the best centers worldwide. Data from the UK suggests that to have sufficient volume to develop a center of expertise for pancreatic cancer, there should be one such center per 2–4 million population.[24] Although issues of geography and the cost of health care can be a challenge for providing such specialist services, data from NSWPCN suggest that in Sydney, Australia, servicing a population of approximately four million, the surgical management of pancreatic cancer occurs in at least 12 separate hospitals. This makes it difficult for any one center to develop sufficient expertise, unless the natural catchment of the hospital covers a large population or develops a reputation that over time draws patients to the hospital to access expertise. Another mechanism is to have a virtual

network of clinicians specializing in the management of patients with pancreatic cancer, which is one of the goals of the NSWPCN: to facilitate communication and interaction across different sites.

In an unselected series of patients who had major pancreatic procedures within the authors' unit at Bankstown Hospital (a University teaching hospital in south-west Sydney, NSW, Australia) from February 1998 to February 2008, there were a total of 427 major elective pancreatic procedures, the majority of which were oncology related. There were 128 Whipple's resections and 108 subtotal (left-sided) pancreatectomies. The remaining 191 cases consisted of 143 elective/semielective biliary/gastric bypasses, 28 pancreatic drainage procedures, and 20 local periampullary duodenal resections. Over this period, the number of major pancreatic procedures increased, with 174 being performed in the last 2 years (51 Whipple, 47 subtotal, and 76 other). Over the 10-year period there was one 30-day mortality and one 90-day mortality in patients who underwent resections, which is equivalent to a mortality rate of 0.9% overall. Both deaths occurred in patients who underwent Whipple pancreaticoduodenectomy, and this equates to a mortality of 1.8% for Whipple pancreaticoduodenectomy in our center. Margin clear (R0) resections were achieved in 74% of cancer cases, and the median survival of patients with histologically-proven pancreatic ductal adenocarcinoma at this point in time is 19.6 months. These data are comparable to figures published by other specialist pancreatic surgical centers around the world.

Treatment of premalignant lesions

Detection and the appropriate management of premalignant lesions in other organs, such as the colon, breast, and cervix, have resulted in improved overall outcomes for the related cancers. There is now compelling evidence of pancreatic ductal adenocarcinomas arising from non-invasive precursor lesions. There are three predominant types: pancreatic intraepithelial neoplasia (PanIN),[75,76] IPMN,[77,78] and MCN. With increasing usage of high-resolution imaging techniques, these cystic precursor lesions are being increasingly identified both in symptomatic and asymptomatic individuals.[79] Early detection and treatment of these precursor lesions (PanIN, IPMN, and MCN) provides the best opportunity to prevent invasive adenocarcinoma of the pancreas. Since pancreatectomy in specialist centers now has a significantly lower mortality, and our understanding of these lesions has increased dramatically in recent times, their surgical treatment has now become highly appropriate. Although PanIN cannot be detected *in vivo* at this time, both IPMN and MCN are macroscopically visible and can be diagnosed using currently-available imaging modalities. MRI and MRCP are still superior to CT in evaluating and characterizing pancreatic cystic lesions.[80]

PanIN

The majority of pancreatic cancers are thought to evolve through a series of hyperplastic and dysplastic ductal lesions termed PanIN. Normal ductal epithelium progresses to invasive adenocarcinomas through a series of histologically-defined precursors (PanIN-1 to PanIN-3), with associated molecular genetic aberrations (Fig. 2). The previous confusion regarding the definition and nomenclature of these pancreatic precursor lesions was resolved at a meeting of a panel of experts held at The Johns Hopkins Hospital (Baltimore, MD, USA) in 2003.[81] PanIN are defined as microscopic papillary or flat, non-invasive epithelial neoplasms arising in the smaller pancreatic ducts. They have columnar to cuboidal cells with varying amounts of mucin and degrees of cytological and

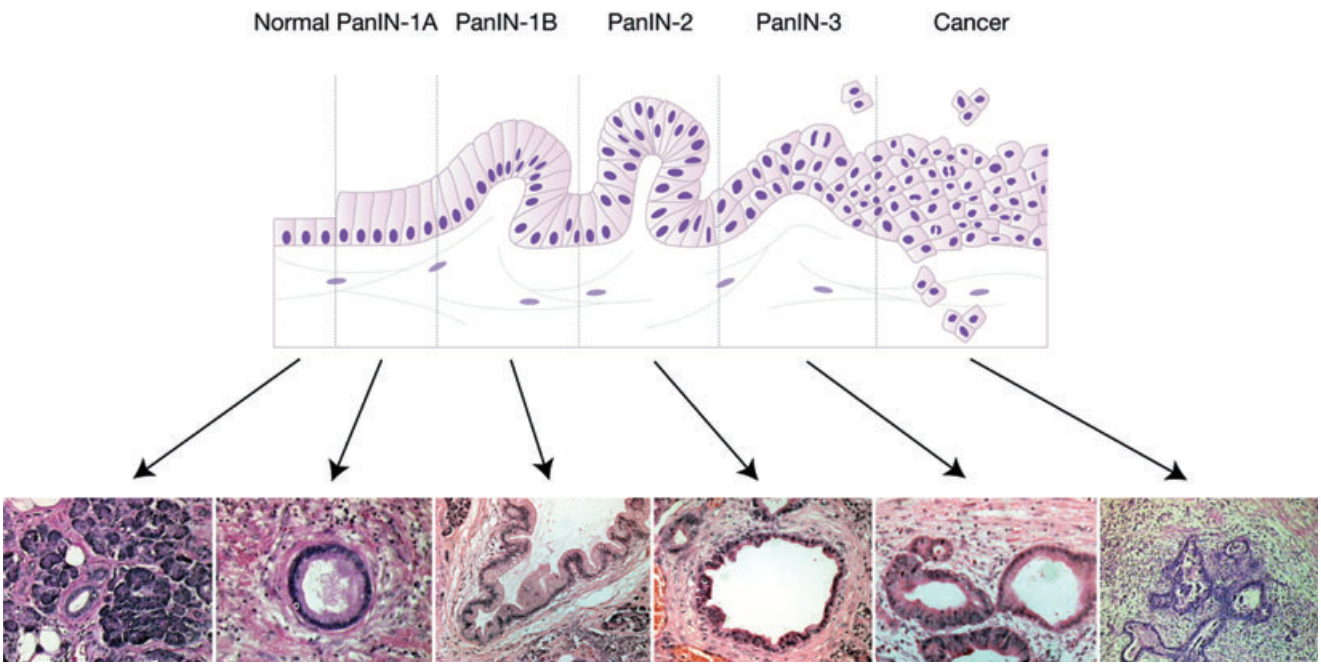

Figure 2 Progression model for pancreatic cancer. The majority of pancreatic cancer is thought to develop through a series of hyperplastic and dysplastic ductal lesions termed pancreatic intraepithelial neoplasia (PanIN).

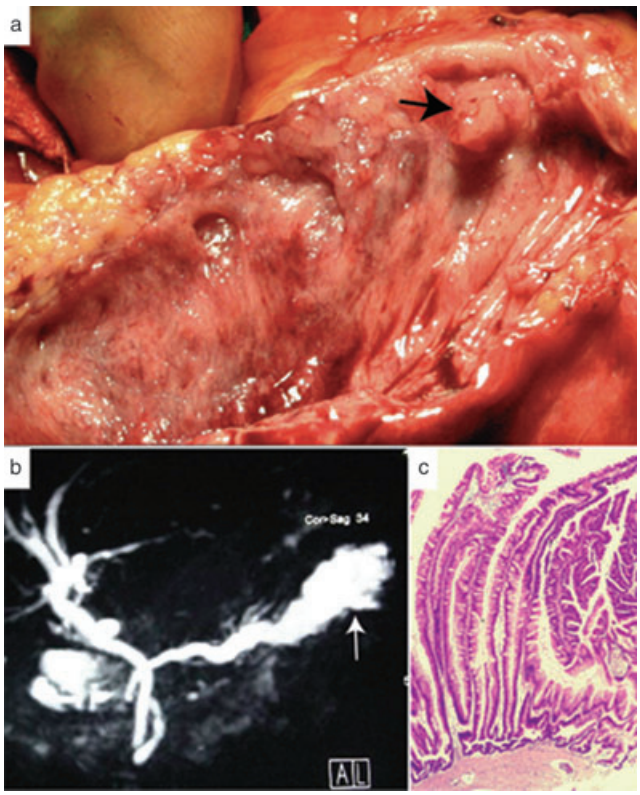

Figure 3 Intraductal papillary mucinous neoplasm (IPMN) of the main pancreatic duct (a) where a relatively small lesion (arrow) can cause significant ductal dilatation due to mucin hypersecretion, as seen on the magnetic resonance cholangiopancreaticography of the same patient (b) Histology (c) demonstrates characteristic tall papillae of IPMN.

architectural atypia. The ability to detect these microscopic lesions in the intact pancreas is a current research priority.

IPMN

IPMN are grossly visible, non-invasive, mucin-producing, predominantly papillary or rarely, flat, epithelial neoplasms arising from the main pancreatic ducts or branch ducts and causing varying degrees of ductal dilatation (Fig. 3).[81,82] IPMN are distinguished from PanIN primarily based on size.[83] Thus most PanIN are <5 mm and most IPMN are >1 cm, but there are occasional exceptions.[81,84]

IPMN occur more often in males with its incidence peaking around 70 years of age. They are located predominantly in the head of the pancreas and account for 5% of pancreatic neoplasms.[85,86] Approximately 35–40% of IPMN are associated with invasive cancer,[87] but even when invasive, resection is associated with a relatively good outcome. In a recent publication combining the experience of 137 patients with IPMN from the Massachusetts General Hospital (Boston, MA, USA) and the University of Verona (Verona, Italy), the 5- and 10-year disease-specific survival for 80 patients with resected adenoma, borderline IPMN, or intraductal papillary mucinous carcinoma without invasion was 100%. This compares to the disease-specific survival of 60% among 57 patients who had IPMN with associated invasive carcinoma.[88] It is generally accepted that complete surgical resection of a non-invasive IPMN greatly reduces the risk of developing invasive cancer.[89]

MCN

MCN are epithelial neoplasms of the pancreas characterized by mucinous epithelium and a distinctive ovarian type stroma. They are the most common (40%) cystic neoplasm of the pancreas. They are seen most frequently in perimenopausal women and are usually located in the body and tail of the pancreas.[90] MCN represent a spectrum of tumors that range from benign, but potentially malignant lesions, to carcinomas with aggressive behavior.[91,92] It is thought that all MCN have the potential to progress to malignancy.[92,93] Once malignant transformation has occurred, they have a similar prognosis to invasive ductal adenocarcinoma.

Early recognition and appropriate management of these precursor lesions is an important step towards improving overall outcomes for pancreatic cancer. The most recent International Consensus Guidelines for the Management of IPMN and MCN of the Pancreas, recommend that all main duct-type IPMN, all symptomatic branch duct-type IPMN, and all MCN should be surgically resected unless there are other contraindications[94] (Fig. 4).

Emerging techniques and future directions in the surgical management of pancreatic cancer

Significant improvement in overall outcome can be achieved with current therapeutic strategies through defining biomarkers of prognosis and therapeutic responsiveness. Significant numbers of patients who have potentially curative operative resections succumb to their disease within 12 months. Similarly, approximately 15% of patients with advanced disease survive over 12 months and have significant issues with stent complications. Stratifying therapies based on biomarker status would better select patients for operative therapy both in a curative and a palliative setting. Significant research efforts are now focused on defining biomarkers of prognosis and therapeutic responsiveness that can be assessed using FNAB,[95–98] and forecast the biology, clinical behavior, and response to therapy of an individual's cancer.

The advantage of treating precursor lesions has been discussed earlier and there is significant effort focused on defining strategies for the early detection of PanIN, IPMN, MCN, and early pancreatic cancer.[99,100] Large-scale, population-based screening is not likely to be feasible. However, an increasing number of high-risk groups for pancreatic cancer, such as those with hereditary pancreatic cancer, patients with new onset diabetes mellitus,[101,102] and potentially those with chronic pancreatitis with a history of heavy alcohol intake and cigarette smoking are being identified. Screening of these patients is justifiable. Further studies are required to identify and define subgroups of patients at risk.

Conclusion

There have been dramatic advances in the understanding and the management of pancreatic disease in the last two decades, particularly in the operative management of pancreatic cancer. Clinicians

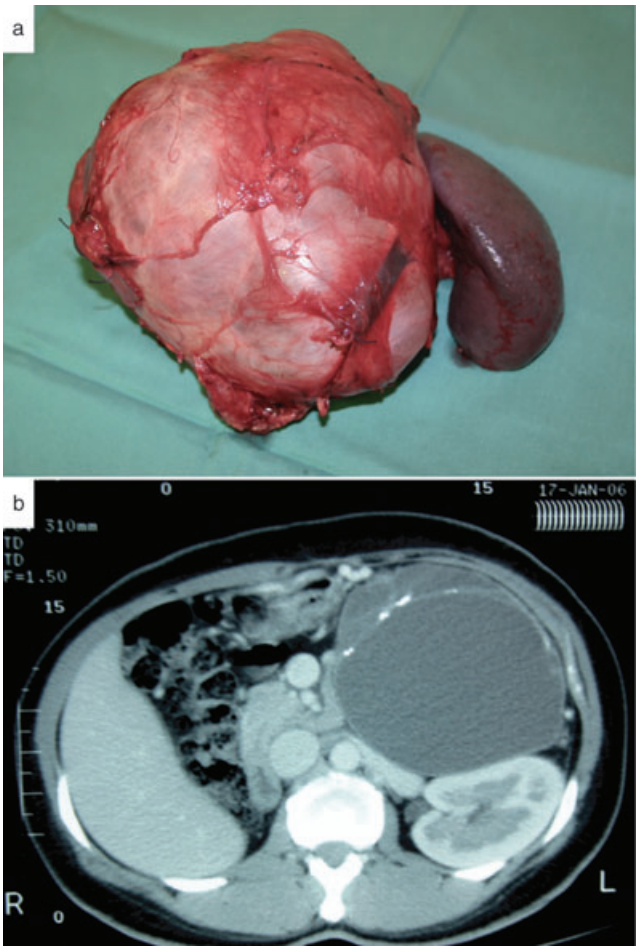

Figure 4 Mucinous cystic neoplasm (MCN) of the pancreatic tail showing the resected specimen (a), and the preoperative CT scan (b).

treating pancreatic cancer should abandon the traditional nihilistic attitude towards this disease and offer patients the most appropriate, up-to-date and evidence-based management to achieve the best possible outcomes.

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